Efficacy of TMS and Cognitive Training in Mild Cognitive Impairment: A Pilot Study

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ABSTRACT

Purpose: Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique with the potential to improve memory. Mild cognitive impairment (MCI), which still lacks a specific therapy, is a clinical syndrome associated with increased risk of dementia. This study aims to assess the effects of deep TMS (dTMS) on a group of 10 patients diagnosed with amnesic MCI.

Methods: We compared the effects of TMS COG treatment (dTMS delivered with H7 helmet for ten daily sessions together with cognitive training of memory and attention), with those of COG treatment (cognitive training alone) of the same duration.

Results: Neuropsychological evaluation at baseline, after TMS COG treatment, after COG treatment and at six months follow up, compared with ANOVA, revealed a significant group-by-time interaction (p = 0.05), favoring the TMS COG treatment for memory tests. The improvement was kept after six months. Other neuropsychological tests were not significantly affected by treatment.

Conclusions: These findings suggest that dTMS might be effective as a therapy for MCI and probably a tool to delay cognitive deterioration.

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Introduction

Mild cognitive impairment (MCI) is an intermediary status between normal aging and early dementia, wherein individuals have subjective cognitive deficits and objective memory impairment, without affecting their daily activities [1, 2].

MCI is not necessarily a prodrome of Alzheimer’s disease (AD), although evidence suggests that patients with the amnesic subtype of MCI (a-MCI) are likely to progress to AD, particularly if amyloid deposition in the brain is detected by PET studies [1, 3, 4]. Episodic memory decline is the most frequent impairment in patients who are at risk (MCI due to AD), with a particular impairment in delayed recall, also impairment in executive abilities, such as decision making, or set shifting behavior may be part of the MCI spectrum, leading to a potential significant impact on everyday functions [5-8]. Memory processing declines with senescence, particularly in episodic memory tasks, which involve encoding and retrieval of information, which are known to be dependent on the integrity of the medial temporal lobe and the interaction with lateral prefrontal cortex (PFC) [9]. Executive functions rely on distributed neural networks that encompass the prefrontal cortex, but also engage the parietal cortex, basal ganglia, thalamus, and cerebellum [10]. For these reasons degenerative diseases, as well as other vascular or toxic and traumatic insults to cortical regions may impact on executive as well as memory functions.

So far there are no evidences of effective pharmacological treatments for MCI [11]. Aerobic exercise in a review of 14 studies, did not reveal significant effects in the majority of them, whereas combined approaches of aerobic exercises, diet changes and cognitive training may have an impact on slowing the decline from normal ageing towards dementia, but they were not tested in patients with MCI [12, 13].

Individual cognitive rehabilitation can be effective for patients with mild-to-moderate dementia with specific functional goals, but its cost-effectiveness requires more evidence [11]. Cognitive training in MCI has been shown to result in improvements on objective memory outcomes immediately following training, however, not on general cognition [14].

Recently neuromodulation techniques proved to be promising in ameliorating several neurocognitive deficits, with mechanisms involving the modulation of cortical circuits, changes in synaptic plasticity and reorganization of the cortex, lasting beyond the stimulation period [15].

Noteworthy, the therapeutic effect of Transcranial Magnetic Stimulation (TMS) on memory was investigated in patients with MCI (a-MCI type) and in patients with Alzheimer’s type dementia (AD). In a recent meta-analysis high frequency repetitive TMS (HF rTMS) over the left DLPFC and Low frequency repetitive
TMS (LF rTMS) over the right DLPFC were found to significantly improve memory functions; furthermore HF rTMS targeting the right inferior frontal gyrus (IFG) significantly enhanced executive functioning. Though, in the majority of the analyzed studies the effects were reported immediately after TMS and in three studies only the authors searched for persisting effects 4 weeks after TMS [16]. It was also shown how multi-site stimulation (mainly bilateral DLPFC) and long-term stimulation appear more effective in producing clinically relevant cognitive improvement in patients with AD. A promising recent study showed that 6 weeks of daily rTMS combined with cognitive training during the same session of treatment, provided significant cognitive benefits on patients with mild AD measured by Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) compared to sham stimulation. Finally it has been reported that the effects of 5-30 consecutive rTMS sessions could last for 4-12 weeks, but longer follow ups have not been investigated so far [17, 18].

Differently from the traditional rTMS -which utilizes 8 shaped coils and provides superficial stimulation in the cortical areas, with fields rapidly decreasing as a function of distance from the coil- deep TMS (dTMS) has been created with the aim of achieving effective stimulation of deep neuronal regions without inducing unbearable fields. This is made possible by the particular Hesed coils (H coils), that have an improved depth penetration and slow rate of electrical field decay [19]. dTMS has been used in major depression and although advocated for other neurological diseases it has never been tested in MCI [20, 21].

For this reason we conducted a pilot case control study on a group of MCI patients to test if dTMS combined with cognitive training may be more useful than cognitive training alone in improving memory and if the effects of dTMS could persist over 6 months follow up.

Methods

We included in this case-control study 10 patients with MCI, diagnosed according to the criterion of the evidence of progressive modest decline in memory or other cognitive domains, based on both subjective concerns and objective measurement, without significant impact on everyday activities (i.e. the individual remains functionally independent, although everyday activities may be more effortful and require compensatory strategies). Patients gave informed consent to participate to the study and the study was conducted according to Helsinki declaration and approved by the Brescia Comitato Etico. Inclusion criteria were: a diagnosis of MCI not earlier than one year, absence of psychiatric illnesses (psychosis or depression requiring medication), absence of other neurological disorders. Exclusion criteria were previous surgery in the brain, epilepsy, cardiac devices (pace maker), CT scan or MRI showing major strokes, brain mass or hydrocephalus, altered function of the thyroid or presence of other metabolic related cognitive impairments (i.e. severe renal or cardiac failure).

Each patient was submitted to two treatments (a case and a control condition), each of them lasting a two weeks period. Ten consecutive daily sessions lasting 30’ were administered in each treatment (Monday to Friday for two weeks). The first treatment consisted of a combined TMS and Cognitive intervention (TMS COG) and the second one, serving as control, consisted of Cognitive intervention alone (COG). This scheme was structured, in order to assess if TMS was more effective than cognitive training, without using the sham dTMS as control condition. In fact dTMS is known to be noisy, to cause involuntary movements, characteristics easily recognizable as “true dTMS”, compared to sham TMS by patients. Time between the interventions was two weeks.

The patients were submitted to detailed neuropsychological evaluation 4 times: at baseline (T0), after one month (T1), during which they were submitted to TMS COG treatment; two months later (T2), during which they were submitted to the COG treatment, and 6 months after the end of this second treatment.

TMS COG

The treatment protocol consisted of 10 consecutive dTMS sessions delivered in two weeks through daily sessions lasting 30’. DTMS was delivered by using the H7 Helmet (Brainsway Ltd.), which has been reported to induce electrical field diagrams including the medial prefrontal cortex and the cingulum [21]. Stimuli were delivered by a Magstim Super Rapid stimulator (Magstim Company, Ltd, Carmarthenshire, Wales, UK). In the beginning of the first session, the optimal spot on the scalp corresponding to a point between Cz and Pz in the electroencephalogram 10-20 system, was localized. This was conducted by delivering single pulses at 60% stimulator output to elicit involuntary contraction of the anterior tibialis. The motor threshold (MT) for each patient was determined by gradually decreasing the intensity of single pulses delivered and defined as the lowest intensity of stimulation able to produce muscle movement in 5 of 10 times. Stimulus intensity was calculated as 80% of feet motor threshold; frequency was 20 Hz, with 50 pulses of 2” duration, and waiting time 20”.

Before each session, patients were asked about possible adverse effects resulting from the previous session. This questionnaire included symptoms such as tiredness, dizziness, nausea, headache, and mood, as well as sleep disturbance agitation, loss of appetite, and irritability. Patients were under the direct supervision of a physician throughout the treatment and any adverse effect or subjective disturbance was immediately recorded and responded to.

During dTMS, in the TMS COG treatment patients were also submitted to cognitive training lasting 30’, consisting of learning and retrieval exercises and of working memory exercises. Learning and retrieval was trained by using stories taken from the Rehacom software, with which has been shown to be useful in ameliorating memory function in brain damaged patients [22, 23]. Each patients started with the easiest exercise of free and cued recall tasks and subsequently was trained, with the help of an experienced neuropsychologist, to reach the more difficult one, in order to obtain a challenging cognitive exercise. Attention, working memory and inhibition control exercises were also used and consisted of symbol cancellation tasks, dual memory tasks, modified Stroop exercises.

COG treatment had the same duration and frequency of the TMS COG. Different versions of memory, learning, working memory and attention exercises were presented to the patients in 10 daily sessions lasting 30’ each.

At each evaluation an extensive neuropsychological assessment was performed at T0, T1, T2 and T3. Tests were administered, where available, in alternative versions, in order to avoid test retest effect, in a quiet environment, by a different neuropsychologist, who was blind about the time and the treatment received by the patients. In addition to MMSE, Short story memory test, Phonemic Controlled Oral word Association test (COWAp), Trial making test, 15 Rey Auditory Verbal learning Test (RAVLT) [28], Rey
Osterrieth complex figure (ROCF) test and Geriatric Depression Scale (GDS) [24-30].

Statistical analysis was conducted by using SPSS software. Each test raw score was recorded over time. In order to assess if some effect of treatment condition (TMS COG or COC) was significant, a repeated-measures ANOVA with Treatment and Time as main factors was performed on each test. Significant main effects and interactions were analyzed by using Bonferroni-corrected pairwise comparisons.

Results
Clinical characteristics of included patients are presented in Table 1. They were four females and six males, their mean age was 79 years. All of them were taking antihypertensive therapy, two of them were also non insulin dependent diabetic, two had lumbar arthrosis. All the patients had brain CT or MR scans, showing in 7 out of 10 brain leucoaraiosis without strokes and various degrees of mild cortical atrophy. Baseline neurological examination was completely normal (no strength, sensory, coordination, balance or cranial nerves impairments detected, normal tendon reflexes).

Table 1: Clinical characteristics of patients

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Education (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>F</td>
<td>71</td>
<td>5</td>
</tr>
<tr>
<td>P2</td>
<td>M</td>
<td>74</td>
<td>5</td>
</tr>
<tr>
<td>P3</td>
<td>F</td>
<td>78</td>
<td>5</td>
</tr>
<tr>
<td>P4</td>
<td>M</td>
<td>81</td>
<td>8</td>
</tr>
<tr>
<td>P5</td>
<td>F</td>
<td>85</td>
<td>13</td>
</tr>
<tr>
<td>P6</td>
<td>M</td>
<td>81</td>
<td>5</td>
</tr>
<tr>
<td>P7</td>
<td>M</td>
<td>76</td>
<td>8</td>
</tr>
<tr>
<td>P8</td>
<td>M</td>
<td>84</td>
<td>13</td>
</tr>
<tr>
<td>P9</td>
<td>F</td>
<td>81</td>
<td>5</td>
</tr>
<tr>
<td>P10</td>
<td>M</td>
<td>81</td>
<td>5</td>
</tr>
</tbody>
</table>

All the patients completed the treatments TMS COG and COG. Except mild headache which was reported in one case after the first two session, no side effects were reported by patients. Two patients did not complete T2 examination and 3 patients did not complete T3 follow up examination (due to travel restrictions in the COVID pandemic or to quarantine in one case).

Mean test’ scores of patients at each examination are presented in Table 2.

Table 2: tests scores at each examination (means ±SD)

<table>
<thead>
<tr>
<th>Test</th>
<th>T0 (n=10)</th>
<th>T1 (n=10)</th>
<th>T2 (n=8)</th>
<th>T3 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>22,70 ± 2,31</td>
<td>23,50 ± 2,22</td>
<td>23,25 ± 2,19</td>
<td>21,71 ± 3,77</td>
</tr>
<tr>
<td>Short story</td>
<td>3,30 ± 2,95</td>
<td>5,35 ± 4,20</td>
<td>5,94 ± 4,14</td>
<td>5,64 ± 3,78</td>
</tr>
<tr>
<td>COWAp</td>
<td>20,70 ± 6,72</td>
<td>22,80 ± 5,25</td>
<td>21,57 ± 6,16</td>
<td>19,00 ± 4,69</td>
</tr>
<tr>
<td>ROCF copy</td>
<td>19,70 ± 8,27</td>
<td>20,20 ± 8,23</td>
<td>22,26 ± 6,43</td>
<td>18,30 ± 6,09</td>
</tr>
<tr>
<td>ROCF recall</td>
<td>3,10 ± 3,20</td>
<td>5,80 ± 2,63</td>
<td>7,00 ± 2,09</td>
<td>5,50 ± 3,30</td>
</tr>
<tr>
<td>TMT A</td>
<td>98,30 ± 54,12</td>
<td>105,67 ± 55,27</td>
<td>94,50 ± 33,32</td>
<td>116,43 ± 30,04</td>
</tr>
<tr>
<td>TMT B</td>
<td>306,30 ± 136,08</td>
<td>333,78 ± 112,61</td>
<td>359,38 ± 67,75</td>
<td>378,43 ± 18,37</td>
</tr>
<tr>
<td>TMT B-A</td>
<td>208,00 ± 103,05</td>
<td>228,11 ± 90,69</td>
<td>264,88 ± 50,99</td>
<td>262,00 ± 22,20</td>
</tr>
<tr>
<td>Clock Drawing Test</td>
<td>4,10 ± 1,96</td>
<td>4,00 ± 1,77</td>
<td>4,63 ± 1,06</td>
<td>5,00 ± 1,15</td>
</tr>
<tr>
<td>RA VLT immediate</td>
<td>25,75 ± 7,19</td>
<td>27,13 ± 10,19</td>
<td>26,50 ± 8,94</td>
<td>27,57 ± 9,29</td>
</tr>
<tr>
<td>RA VLT delayed recall</td>
<td>1,25 ± 1,75</td>
<td>2,63 ± 2,67</td>
<td>5,14 ± 3,24</td>
<td>3,71 ± 2,56</td>
</tr>
<tr>
<td>GDS</td>
<td>9,30 ± 7,38</td>
<td>9,20 ± 7,02</td>
<td>10,63 ± 6,41</td>
<td>11,86 ± 7,31</td>
</tr>
</tbody>
</table>

MMSE = Mini-mental State Examination; COWAp = Phonemic Controlled Oral Word Association; ROCF = Rey-Osterrieth complex figure; TMT = Trial Making Test; RA VLT=Rey Auditory Verbal Learning Test; GDS = Geratric Depression Scale.
Two-way analysis of variance (ANOVA) for repeated measures showed a significant effect of treatment (TMS COG and COG) x time of examination (T0,T1,T2,T3) for Short story test (F(3,18)=3.78, p=0.02). Post hoc analysis showed a statistically significant improvement of scores between T0 and T1 (mean score at T0=3.30 and at T1=5.35; p = 0.026), between T0 and T2 (mean score at T0=3.30 and at T2=5.94; p=0.028), but not significant differences between T1 and T2 or between T2 and T3 (mean score at T2=5.94 and at T3=5.64).

For ROCF recall test, repeated measures ANOVA showed a significant effect of treatment x time of evaluations (F(3,18)=7.7, p=0.001), with statistically significant improvement of scores between T0 and T1, T2, T3 (mean score at T0=3.10 and at T1=5.80; p=0.0025; mean score at T0=3.10 and at T2=7; p=0.002; mean score at T0=3.10 and at T3=5.50; p=0.005), but no significant differences between T1 and T2 or T2 and T3. In summary both verbal and non verbal memory tests resulted to be significantly improved after TMS COG, compared to baseline, without any further significant change after COG treatment and at follow up (Figure 1).

Figure 1: Mean scores in Short story test and Rey Oster Reith Complex Figure Recall over time

For all the other tests repeated measures ANOVA did not show any significant treatment x time of evaluation effect.

Discussion

The results of our pilot study show that memory tests are significantly improved by dTMS delivered with the H7 Helmet that the improvement lasts over six months, whereas the other neuropsychological tests including depression measures are not significantly modified by this treatment. In particular, verbal memory and ROCF recall significantly ameliorate after TMS, but not after the cognitive training alone (COG). The results persist over time, as at six months follow up, there is no significant difference in scores of memory tests, compared to T1 examination (after dTMS). Although conducted on a limited group of patients, who served as cases and controls and without a randomized design, these data support the superiority of dTMS combined with cognitive training on cognitive training alone in inducing an improvement in memory function. This is confirmed by the absence of further improvement in memory functions after COG treatment, which could have been expected in the case of a practice effect (similar training exercises were administered during both treatments) and points to a specific and longstanding effect of dTMS on memory function.

Unexpectedly, in our sample of patients, we were not able to find improvements in other cognitive functions, neither after dTMS nor after cognitive training. This may be interpreted as a functional stimulation of specific brain structures involved in memory, provided by the dTMS, noteworthy the cingulum and the related prefrontal and subcortical regions. Depression scores were not affected by treatments in our group of patients as well; on the other hand they were not particularly depressed at the beginning of the study and the device applied for dTMS in our study was different from that one approved for depression by FDA [20].

rTMS has been shown to significantly improve several cognitive abilities in AD including language, memory and executive functions, although, in the published studies, the variability in the sites of stimulation, the concomitant assumption of anti cholinesterase treatments, as well as the variability in the number of sessions and the association with cognitive training could have biased the results, which are not consistent [31]. Data from meta analyses point to more effective results with multiple sites of rTMS stimulation, involving the DLPFC (which is the more frequently investigated site of stimulation in rTMS studies), though the long term efficacy of the treatment has not been addressed so far [16, 17].

Deep TMS, which has been less investigated than rTMS, is assumed to have the advantage of a wider and deeper site of stimulation and could be better suited for reaching structures, such as the cingulum, that are known to be important for memory function [31]. Interestingly, studies on the role of rTMS in episodic memory, support the involvement of a more distributed neural network sustaining this function, including the temporal lobes and parietal cortices [32]. Furthermore, it has been suggested that stimulating the medial PFC could be advantageous because it is part of the default-mode network, which is important for memory functions [33]. These observations suggest that using dTMS might be useful in order to address more diffuse cortical networks involved in memory function [34]. Avrame et al. reported improved cognition in 60% of 11 AD patients by using dTMS with H2 helmet, which is considered useful for stimulating the prefrontal cortex [35]. Though, they did not have a control condition and did not perform a follow up evaluation. Our study support the utility of dTMS with H7 helmet in treating memory impairment of patients with aMCI, with longstanding effects, although further studies with larger sample of patients, possibly better characterized with CSF or imaging biomarkers, are needed to confirm these results.

Furthermore studies involving cohorts of MCI patients followed over years are needed, to clarify whether TMS is able to delay the conversion of mild cognitive decline into AD.

Declarations

The Authors declare no conflict of interest, declare that the research has been conducted without funding and that all the data are available on request of qualified scientists.

References


